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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,231	01/22/2002	Staffan Nilsson	000510-007	7956

7590 11/28/2005

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EXAMINER	
DEJONG, ERIC S	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 11/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,231	NILSSON ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-20,22-28,32-34,38 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,29-31,35-37,39,40 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Claim Objections

The objection of claims 21 and 29-31 is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21, 29, 30, 35-37, 40, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Schober et al. in further view of Izmailov et al. This rejection is maintained and reiterated from the previous Office action.

The instant claims are drawn to methods and systems for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned droplet, and one or more means of detecting nucleation tendency in the at least one droplet.

[Claims 21, 29, 30, 35-37, 40, 44, and 45]: Ishikawa et al. set forth the methods and systems for the development of acoustic levitators for containerless protein crystallization (See Ishikawa et al., Abstract), with the cited goal of evaluating the efficacy of levitators in microgravity environments by first assaying the feasibility of such levitators in a 1-g environment as containerless crystallization systems (a method for screening crystallization conditions or amorphous stage conditions for a molecule). Test systems included the employment of a sonic levitator and several 25 μl sample droplets of lysozyme protein at various concentrations and salt conditions (at least one levitator for positioning at least one droplet). See Ishikawa et al., page 334, column 1, line 8 through page 335, column 2, line 6. The system employed a charge coupled detector camera (CCD) as a means for detecting and monitoring crystallization conditions in the levitated droplets. See Ishikawa et al., Figure 1. However, Ishikawa et al. discloses that

droplets contained an oversaturated sample of lysozyme with variable levels of NaCl, and does not fairly teach delivering at least one substance to the levitating droplet.

Schober et al. taken as a whole teaches using a piezoelectric dispenser for the accurate microdispensation of biochemically relevant solutions and suspensions. Schober et al. also teaches that such piezoelectric devices have been developed and applied in industrial applications, but are well suited for biological sample applications. See Schober et al., page 328, lines 10-19. Further, Schober et al. teaches that manual and mechanical means of dispensing liquids are insufficient for accurate sample dispensation of very small volumes, but the disclosed piezoelectric transducer device provides dispensation of very small volumes without any detectable impact on the biological function of dissolved or suspended molecules. See especially Schober et al., Abstract. However, Schober et al. does not fairly teach the delivery of substances from a piezoelectric dispenser to a levitated droplet.

Izmailov et al. sets forth methods and systems for preparing and studying highly supersaturated solutions suspended in a levitator trap. See Izmailov et al., Abstract. Izmailov et al. employ a piezoelectric dispenser to deliver highly accurate volumes of microdroplets to a sample droplet levitated in the center of a spherical void electromagnetic levitator trap (SVELT) in order to investigate homogeneous nucleation conditions. See Izmailov et al., Figure 1 and page 52, column 1, lines 4-53.

Therefore, taken in view of Schober et al. in further view of Izmailov et al., it would have been obvious to one of skill in the art to employ a piezoelectric transducer device to accurately deliver substances to the levitated droplet in the methodology and systems as disclosed by Ishikawa et al. for the optimized development and evaluation of acoustic levitators for containerless protein crystallization.

Claims 31, 42, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Schober et al. in further view of Izmailov et al. as applied to claims 21, 29, 30, 35-37, 40, 44, and 45 above, and further in view of Arnowitz et al. This rejection is maintained and reiterated from the previous Office action.

[Claims 31 and 46]: As presented above, Ishikawa et al. taken in view of Schober et al. taken in further view of Izmailov et al. sets forth the employment of a piezoelectric transducer device to deliver accurate substances to the levitated droplet in conjunction with the methodology and systems as disclosed by Ishikawa et al. in the development of acoustic levitators for containerless protein crystallization. However, neither Izmailov et al, Schober et al., nor Ishikawa et al. fairly teach the crystallization of a nucleic acid, DNA, RNA, an oligonucleotide or a polynucleotide.

Arnowitz et al. sets forth methods and systems for controlling dynamic, reagent induced transformation of multiple biological samples in the optimization of crystallographic conditions. See Arnowitz et al., paragraphs 001 and 0014. Further, Arnowitz et al. discloses that suitable samples for use in the disclosed crystallization methodologies are small and large biomolecules which include macromolecules, proteins, nucleic acids (broadly construed as oligonucleotides and polynucleotides), ligands and drugs. See Arnowitz et al., paragraph 0017.

Therefore, taken in view of Arnowitz et al., it would have been obvious to one of skill in the art to employ the methodology and systems set forth by Ishakawa et al. in view of Izmailov et al. in further view of Schober et al. for the crystallization of nucleic acids, polynucleotides and oligonucleotides.

[Claim 42]: As presented above, Ishikawa et al. in view of Izmailov et al. in further view of Schober et al. sets forth the employment of a piezoelectric transducer device to deliver accurate substances to the levitated droplet in conjunction with the methodology and systems as disclosed by Ishikawa et al. in the development of acoustic levitators for containerless protein crystallization. However, neither Izmailov et al., Schober et al., nor Ishikawa et al. fairly teach delivery to the at least one levitating droplet by the dispenser a substance that influences nucleation tendency.

Arnowitz et al. sets forth methods and systems for controlling dynamic, reagent induced transformations of multiple biological samples being crystallized. See Arnowitz et al., paragraphs 0001 and 00014. The disclosed supports a deliver system by which multiple reagents effecting nucleation conditions can be delivered to samples that are undergoing crystallization. See Arnowitz et al., paragraph 0072, 0078, and 0082.

Therefore, taken in view of Arnowitz et al., it would have been obvious to one of skill in the art to deliver a substance that effect nucleation conditions to the levitating droplet, as taught by Ishikawa et al. taken in view of Izmailov et al. in further view of Schober et al., in order to enhance the dynamic control of crystallization conditions in a sample.

Claims 39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Izmailov et al. in view of Schober et al. in further view of Arnowitz et al. as applied to claims 21, 29, 30, 31, 35-37, 40, 42, and 44-46 above, and further in view of Schwartz et al. This rejection is maintained and reiterated from the previous Office action.

[Claims 39 and 43]: As presented above, Ishikawa et al. taken in view of Schober et al. taken in further view of Izmailov et al. sets forth the employment of a piezoelectric transducer device to deliver accurate substances to the levitated droplet in conjunction with the methodology and systems as disclosed by Ishikawa et al. in the development of acoustic levitators for containerless protein crystallization. Further, the levitated droplet as disclosed by Ishakawa et al. is free floating without obstruction from nearly 360°, and

thus can be illuminated by light from an illumination source from nearly any direction (broadly construed as the droplet can be illuminated by rotating light). Further, Arnowitz et al. teaches the use of multiple optical sensors for one or more features of light that have traveled through a sample currently undergoing crystallization. However, neither Schober et al., Arnowitz et al., nor Ishikawa et al. fairly teach the detection of nucleation tendency in context of crystal formation by multi-angle light scattering in combination with Raman spectroscopy.

Schwartz et al. teaches the specific use of Raman spectroscopy for monitoring protein concentration to report on nucleation condition of a sample being crystallized. See Schwartz et al., Abstract. Further, Schwartz et al. asserts that Raman spectroscopy is ideal for biochemical experiments in aqueous media (see Schwartz et al., Introduction, final paragraph) and that the disclosed application of the technique greatly enhances the process of determining the necessary criteria for protein crystal growth.

Therefore, taken in view of Schwartz et al., it would have been obvious to one of skill in the art to employ Raman spectroscopy and the sample detection methodologies disclosed by Arnowitz et al. with the methodologies and systems as set forth by Ishikawa et al. taken in view of Schober et al. and Arnowitz et al. in order to enhance the process of determining the necessary criteria for protein crystal growth.

Response to Arguments

Applicant's arguments filed 09/13/2005 have been fully considered but they are not persuasive.

In response to the rejection of claims under 35 U.S.C. 103(a), applicants argue that the applied references do not suggest or motivate combination so as to rendered the instantly claimed invention obvious.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, applicants arguments are not directed to the motivation to combine the instant references on pages 6, line 12-16, page 7, lines 8-14, page 8 lines 9-13 and page 9, line 16-20 of the previous Office action, which are further reiterated above.

In regards to independent claim 22, applicants specifically argue that Ishikawa et al. discloses that vibration-induced streaming within the droplet in an acoustic levitator prevents crystallization which teaches away from the presently claimed invention. In response, the Examiner points out that no specific citation from Ishikawa et al. was provided in applicants response. Upon further review of said reference, the Examiner acknowledges that indeed suggests that acoustic affects crystallization. Page 337, column, first paragraph states:

> "With the acoustic levitator, crystals did not form in any solution. This suggests that acoustic vibration affects crystallization. Levitation of a liquid droplet in a 1-g environment requires a minimum field of 150dB. The droplet was stable, but it seems that vibration induced streaming prevented crystallization."

Contrary to applicants argument, Ishikawa does not teach that vibration induced streaming within a droplet will prevent crystallization in all cases. In fact, the authors explicitly state that there is an observable acoustic affect in a 1-g environment and with a minimum sound field of 150dB. The intended applications of the such levitating crystallization methods are stated also being directed to microgravity environments (see Ishikawa et al., page 300, column 1, lines 1-14). As such, the adverse crystallization affects would be diminished in microgravity environments as a much lower field strengths would be utilized. One of ordinary skill in the art would readily recognize and accommodate such disclosed limitations the disclosed methods and systems.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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EDJ EDJ

17 November 2005

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER